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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/036,724	03/06/98	FERRONE S	FER-1

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EXAMINER	
NICKOL,G	
ART UNIT	**PAPER NUMBER**
1642	14

DATE MAILED: 10/19/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/036,724	Applicant(s) FERRONE ET AL.	
	Examiner Gary B. Nickol Ph.D.	Art Unit 1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspond nce address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 August 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disp sition of Claims

4)☒ Claim(s) *1-56* is/are pending in the application.

4a) Of the above claim(s) *11,12,14-16,19 and 24-55* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10,13,17,18,20-23 and 56* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of Group I (Claims 1-30 and 56) in Paper No. 13 is acknowledged. Claims 1-56 are pending. Claims 11-12, 14-16, 19, and 24-55 have been withdrawn from further consideration by the examiner under 37 CFR 1.142(b) as being drawn to non-elected inventions. Claims 1-10, 13, 17-18, 20-23, and 56 are pending and are currently under consideration.

Claim Objections

Claims 20-23 are objected to for minor grammatical errors in reciting "wherein the a molecule".

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-10, 13, 17-18, 20-23, and 56 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-10, 13, 17-18, 20-23, and 56 are rejected as vague for reciting "treating" in Claims 1 and 56. It is not clear if "treating" the mammal comprises curing the mammal or

merely comprises a step of administration. This rejection can be obviated by amending the claims to recite "comprising administering to the mammal an effective amount ..".

Claims 1, and 17-18 are further rejected as vague for reciting "the immunogen is expressed on an antigen presenting cell not native to the mammal" in claim 17. It not clear which product is actually "non-native" to the mammal. Is the antigen presenting cell foreign or is the immunogen foreign?

Claim 13 is rejected as vague and indefinite for reciting "substantially". The term "substantially" is not defined by the claim, and the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-10, 13, 17-18, 20-23, and 56 rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention.

Factors to be considered in determining whether undue experimentation is required, are summarized in *Ex parte* Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or

guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The claims are broadly drawn to inhibiting an unwanted angiogenic condition in a mammal in need thereof comprising treating the mammal with an effective amount of an immunogen such that the immunogen causes an immune response wherein the immune response is directed against a "molecule" that induces angiogenesis in the mammal.

The specification teaches (page 9, line 2) that the immunogens of the invention unexpectedly induce an effective immune response when properly presented to the immune system wherein the immune system preferably inhibits or eliminates the pathological condition associated with angiogenesis, such as growth of cancer cells. The specification teaches (page 9, 2nd paragraph) that the immunogens of the invention may be any angiogenic molecule associated with the process of angiogenesis. The specification further teaches (page 14, 1st paragraph) that "an immune response means production of antibodies, i.e. humoral, and/or a cell-mediated response, such as a T-cell response including helper and cytotoxic T cell responses".

The claims are not enabled because the specification does not provide guidance and objective evidence that the claimed method would predictably inhibit an unwanted angiogenic condition (including the inhibition of tumor growth which reads on the treatment of cancer) in vivo by treatment with an effective amount of an immunogen.

In particular, there is no objective evidence or guidance regarding administration of the immunogen and or a vector that expresses an immunogen in vivo which elicits any immune response. Those of skill in the art of cancer vaccines recognize that active specific

immunotherapy may hold promise for the future, but is rather unpredictable. According to Spitler, (Cancer Biotherapy, v10(1), 1995, pp. 1-3) ask a practical oncologist what they think about cancer vaccines and one would likely get the following response "cancer vaccines don't work.". Asking a venture capitalist or the director of product development at a large pharmaceutical company the same question would also generate the same response (column 1). Further, although directed to tumor antigens, the teachings of Bellone et al. (Immunology Today, v20 (10), 1999, pp.457-462) relate to the presently claimed invention in that Bellone et al. summarize the current state of the art of peptide immunotherapy including clinical trials where "there is usually a poor correlation between induction of specific T-cells and the clinical responses" (page 457, 2nd column). Further, Bellone et al. teach the disadvantages of peptide cancer immunotherapy in that (1) there is no direct evidence for a role in tumor rejection, (2) the therapy is applicable to few patients, (3) risk of generating tumor escape mutants, and (4) risk of autoimmune reactions (page 461, Box 1). Further the treatment of cancer, in general, is at most unpredictable as underscored by Gura (Science, v278, 1997, pp.1041-1042) who discusses the potential shortcomings of potential anti-cancer agents including extrapolating from in-vitro to in-vivo protocols, the problems of drug testing in knockout mice- particularly strains which have tumor suppressor gene knockouts, and problems of clonogenic assays. Indeed, since formal screening began in 1955, thousands of drugs have shown activity in either cell or animal models, but only 39 that are used exclusively for chemotherapy, as opposed to supportive care, have won approval from the FDA (page 1041, 1st column) wherein the fundamental problem in drug discovery for cancer is that the model systems are not predictive.

Also, with regards to Claims 1 and dependent claims 17 and 18- there is insufficient guidance and objective evidence that the method will predictably treat an unwanted angiogenic condition wherein the immunogen is expressed on an antigen-presenting cell (APC) not native to the mammal. The specification teaches (page 18) that the immunogen may be presented to the immune system by a vehicle, such as on the surface of an APC. However, as written, it is not clear if the APC is foreign or if the immunogen is foreign. If the APC is foreign, there is not enough evidence in the specification that the host immune system response will be directed against native angiogenic molecules and not the foreign cells themselves. Secondly, if the immunogen is foreign, there is not enough guidance in the specification that the immune response will be directed against native angiogenic molecules and not the foreign peptide. The specification refers to U.S. Patent No. 5597563- however the teachings of U.S. Patent No. 5597563 are concerned with inducing antigen-specific immune tolerance and not eliciting an immune response to against an angiogenic molecule.

Moreover, the disclosure does not provide working examples wherein all of the steps required to practice the method are employed. Lack of working examples is given added weight in cases involving an unpredictable and undeveloped art such as the treatment of cancer. In the instant case, the claims are so broadly drawn, the guidance is so limited, and the art is so unpredictable that skilled artisan is presented with a multitude of un-linked alternatives with no guidance as to which will enable use of the invention as claimed.

Essentially, the specification provides insufficient guidance with regard to theses issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict the efficacy of

the claimed invention with a reasonable expectation of success. For the above reasons, it appears that undue experimentation would be required to practice the claimed inventions with a reasonable expectation of success.

If applicant were able to overcome the 112 1st paragraph enablement rejection above, the following claims would still be rejected:

Claims 1-10, 13, 17-18, 20-23, and 56 are further rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of inhibiting an unwanted angiogenic condition in a mammal in need thereof comprising treating the mammal with an effective amount of an immunogen that is modified to improve immunogenicity wherein such administration causes an immune response against a molecule that induces angiogenesis in the mammal, does not reasonably provide enablement for the method as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The claims are broadly drawn to inhibiting an unwanted angiogenic condition in a mammal in need thereof comprising treating the mammal with an effective amount of an immunogen such that the immunogen causes an immune response wherein the immune response is directed against a "molecule" that induces angiogenesis in the mammal.

The specification teaches (page 9, line 2) that the immunogens of the invention unexpectedly induce an effective immune response when "properly" presented to the immune system wherein the immune system preferably inhibits or eliminates the pathological condition

associated with angiogenesis, such as growth of cancer cells. The specification further teaches (page 1), that such methods of immunotherapy against angiogenic molecules include modification of immunogens to cause an immune response.

One cannot extrapolate the teachings of the specification with the scope of the claims because, as written, the claims include eliciting an immune response with an "unmodified" immunogen, including native immunogens or "self" proteins. Thus, it appears that modification of the immunogen is an essential step in eliciting an immune response. Further, those of skill in the art of immunotherapies recognize that administration of immunogens to mammals must overcome the immune tolerance of "self" proteins. Presumably, it would be difficult to elicit an immune response to such angiogenic molecules with a vaccine based on autologous or syngeneic immunogens because of the immune tolerance acquired during the development of the immune system.

In view of the above, it appears that undue experimentation would be required to practice the claims as broadly written.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 1-7, 9-10, 13,17, 23, and 56 are rejected under 35 U.S.C. 102(e) as being anticipated by Nacy *et al.* (U.S. Patent No. 5,919,459)

Nacy *et al.* teach a method of inhibiting an unwanted angiogenic condition including tumors, arthritis, macular degeneration, and psoriasis (abstract, and column 1, lines 50-58) in a mammal or human in need thereof comprising treating the mammal with an effective amount of an immunogen (or vector that expresses an immunogen) such that the immunogen causes an immune response against a molecule that induces angiogenesis in the mammal (column 2, lines 14-35; column 5, lines 12-17; column 6 lines 10-26). Nacy *et al.* further teach that the immunogen is an antigen that is native to the mammal, and that is modified to improve immunogenicity wherein the antigen is conjugated to an immunogenic compound or is combined with an adjuvant (column 2, lines 66-67; column 3, lines 6-33) or is substantially purified (column 6, lines 40, and 63-67). Nacy *et al.* further teach that the immunogen is expressed on an antigen-presenting cell not native to the mammal (column 5, lines 60-64; column 6, lines 10-36) wherein the specification teaches (page 18, 2nd paragraph) that the definition of antigen presenting cells is non-limiting includes recombinant eucaryotic cells. Nacy *et al.* further teach that the molecule that induces angiogenesis is VEGF (column 3, lines 34-47).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gary B. Nickol Ph.D. whose telephone number is 703-305-7143. The examiner can normally be reached on M-F, 8:30-5:00 P.M..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached on 703-308-3995. The fax phone numbers for the

organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Gary B. Nickol, Ph.D.
Examiner
Art Unit 1642

GBN
October 13, 2001

SUSAN UNGAR PH.D
PRIMARY EXAMINER

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